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# Long-Term Fosfomycin-Tromethamine Oral Therapy for Difficult-To-Treat Chronic Bacterial Prostatitis

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**This is a retrospective study of 15 difficult-to-treat (i.e., exhibiting previous failure, patient side effects, or resistance to ciprofloxacin and co-trimoxazole) chronic bacterial prostatitis infections (5 patients with multidrug-resistant *Enterobacteriaceae* [MDRE]) receiving fosfomycin-tromethamine at a dose of 3 g per 48 to 72 h for 6 weeks. After a median follow-up of 20 months, 7 patients (47%) had a clinical response, and 8 patients (53%) had persistent microbiological eradication; 4/5 patients with MDRE isolates achieved eradication. There were no side effects. Fosfomycin-tromethamine is a possible alternative therapy for chronic bacterial prostatitis.**

Chronic bacterial prostatitis (CBP) is a troublesome disease, showing an overall clinical and microbiological response rate to fluoroquinolones, the antibiotics of choice, of only 60% (1–4). In CBP caused by *Escherichia coli*, the reported resistance rates are 11% to ciprofloxacin and 20% to norfloxacin (5). Co-trimoxazole is an alternative antibiotic option, but its cure rates are lower than those of other drugs (1, 4). The resistance rate to co-trimoxazole is high in patients with urinary tract infections (UTI) (around 34% in Spain) (6), and reported resistance in *E. coli* CBP is 24% (5). Other antibiotics are usually ineffective due to poor prostatic penetration; hence, there may be no effective antibiotic therapy for some patients (1).

Fosfomycin-tromethamine (FT) has broad-spectrum antimicrobial activity and is useful for treating lower UTI caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (7–10). Mean fosfomycin levels in the uninflamed peripheral prostate region after 3 g of FT were found to be >4 μg/g of tissue in 70% of patients (11). This value is higher than the MIC breakpoint of many uropathogens. In addition, FT proved useful in 2 cases of multidrug-resistant *Enterobacteriaceae* (MDRE) prostatitis (12).

(This study was presented in part as poster no. 838 at the XIX Congreso de la Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica [SEIMC], 28 to 30 May 2015, Seville, Spain [13].)

In this retrospective study, we assessed the efficacy of FT as an alternative therapy for patients with difficult-to-treat CBP. The inclusion criteria were a diagnosis of CBP, failure of prolonged antibiotic therapy, and no possibility of fluoroquinolone or co-trimoxazole use due to resistance, failure, or side effects (Fig. 1). All patients had been treated and followed up in our UTI outpatient clinic (January 2010 to July 2014) by one of the authors (C.P.). The study was approved by the hospital ethics committee and Spanish Drug Agency (approval VDH-FOS-2014-01).

A diagnosis of CBP was established when all 4 criteria were met: (i) history of CBP, defined as ≥1 previous symptomatic episode of bacterial prostatitis of ≥4 weeks duration or ≥2 episodes of any duration in the preceding 12 months; (ii) current symptoms of prostatitis; (iii) absence of genitourinary abnormalities on ≥1 urologic ultrasound assessment; and (iv) current laboratory evidence of infection, including positive Meares-Stamey test result (14), positive semen culture, or ≥2 positive urine cultures with the same microorganism performed ≥1 month apart, in which a typical uropathogen was detected.

Semen culture was considered positive when (i) bacteria were found in the semen sample, and either (ii) no bacteria were detected in the first voided urine (VB1) or midstream-voided urine (VB2) sample, or the bacterial colony count in the semen sample was ≥10 times that in the VB1 and VB2 specimens. Urine culture was considered positive with colony counts of $\geq 10^3$ CFU/ml.

Susceptibility to fosfomycin, co-trimoxazole, and ciprofloxacin was evaluated by disk diffusion or Etest, according to CLSI recommendations (15), up to 2014. In April 2014, our microbiology department implemented the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). ESBL was diagnosed by phenotypic confirmatory methods based on their *in vitro* inhibition by clavulanic acid (double-disk synergy test and disk diffusion with cefotaxime and ceftazidime alone and in combination with clavulanic acid). An acquired (plasmidic) AmpC strain was suspected in strains with resistance to cefotaxime or ceftazidime but susceptible to cefepime. The phenotypic confirmatory tests used in the laboratory were based on their *in vitro* inhibition by boronic acid. All cases were confirmed by PCR techniques. *Enterobacteriaceae* nonsusceptible to at least 1 agent in ≥3 antimicrobial categories were considered MDRE (16).

Previous antibiotic failure was established when symptoms

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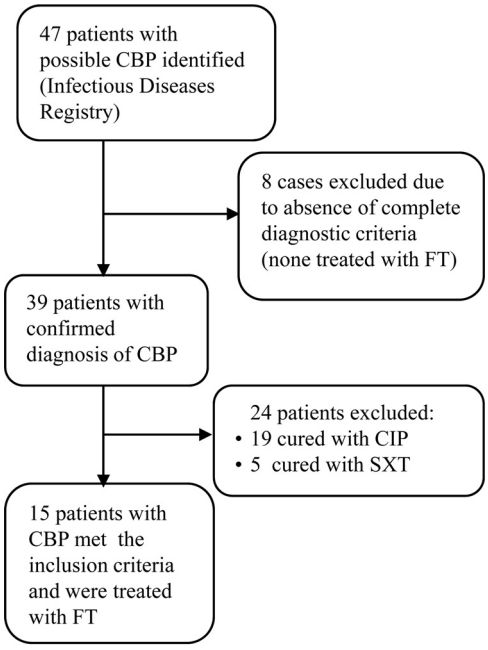


CBP, chronic bacterial prostatitis; CIP, ciprofloxacin; FT, fosfomycin-tromethamine; SXT, trimethoprim-sulfamethoxazole.

**FIG 1** Flow diagram of patients included in the study.

persisted and cultures tested positive in patients treated with ≥4 weeks of ciprofloxacin (500 mg/12 h) or ≥6 weeks of co-trimoxazole (160 mg/800 mg/12 h). All patients included received FT at a dose of 3 g every 48 to 72 h for 6 weeks, and all were followed up for ≥1 year in the UTI outpatient clinic.

Clinical response to FT was defined as resolution or appreciable improvement in pretreatment signs and symptoms, with no additional antibiotic therapy during follow-up. Clinical failure was established when symptoms persisted after 2 weeks of treatment or recurred during follow-up.

The microbiological eradication rate was determined based on a negative Meares-Stamey test result or 2 negative semen cultures at 1 month and 6 months after the completion of treatment. Microbiological failure was defined as persistent isolation of the same microorganism in the follow-up cultures. Superinfection was defined as infection by a new pathogen. Side effects were specifically recorded in all patients. The data for quantitative variables are expressed as the median and interquartile range (IQR), and the data for discrete variables are expressed as the number and percentage.

Over the study period, 15 CBP patients (median age, 54 years; IQR, 44 to 49 years) received FT. The clinical and microbiological data are shown in Table 1. All patients had experienced recurrent UTI (median, 4 prior episodes; IQR, 4 to 9 episodes) and had failed ≥1 previous prolonged antibiotic treatment (median, 6 weeks; IQR, 4 to 8 weeks).

The microorganisms isolated included *E. coli* in 14 (93%) patients, MDRE in 5 (37%) patients (4 ESBL producers and 1 CMY-type AmpC β-lactamase producer), and *Klebsiella oxytoca* in 1 patient.

Primary ciprofloxacin resistance was detected in 5 isolates. Of 10 isolates from ciprofloxacin-treated patients with clinical failure, 5 isolates showed secondary resistance. Primary co-trimoxazole resistance was found in 8 isolates. None of the 4 co-trimoxazole-treated patients with clinical failure showed secondary resistance. In 3 co-trimoxazole-susceptible isolates, co-trimoxazole was not used because of allergy in 2 patients and gastrointestinal intolerance in 1 patient.

All patients except 1 (case 1, initially given 7 days of ertapenem) were treated with oral FT alone for 6 weeks. In 13, FT was administered every 72 h. In an attempt to improve efficacy, the last 2 patients (cases 14 and 15) received FT every 48 h.

After a median follow-up of 20 months (IQR, 14 to 36 months), 7/15 (47%) patients showed clinical cure. Microbiological eradication at 1 and 6 months was documented in 9/15 (60%) and 8/15 (53%) patients, respectively. Among the 7 microbiological failures, 1 patient had a persistent infection, and 6 patients had clinical relapse. One microbiological failure (case 9) retreated with FT at a dose of 3 g/48 h for 8 weeks relapsed. Only 1 patient with microbiological failure developed fosfomycin resistance. Among 5 MDRE CBP, 4 cases had sustained clinical cure and microbiological eradication at a median of 29 months. Among 6 cases with prostatic calcifications, 2 cases cured, 1 case persisted, and 3 cases relapsed. There were no gastrointestinal side effects or allergic reactions.

Patients failing FT were treated with ≥12 weeks of ciprofloxacin (3 patients) or co-trimoxazole (3 patients) for susceptible microorganisms or long-term suppressive antibiotic regimens (50 mg/day nitrofurantoin in 1 patient); these patients currently are in the follow-up period.

In the experience reported, half our CBP patients failing prolonged first-line antibiotic treatments and given FT at a dose of 3 g every 48 to 72 h for 6 weeks achieved clinical cure and microbiological eradication; nonetheless, the other half failed. Apart from the recognized difficulty in achieving cure in CBP patients failing first-line therapies, several factors may have contributed to this lack of response. The optimal use of FT is hindered by the absence of defined MICs for conditions other than lower UTI (≤64 μg/ml) (15). Our 2014 susceptibility data for *E. coli* uropathogens using Vitek 2 showed that 8,003/8,291 (96.5%) isolates were susceptible to fosfomycin at MICs of ≤16 μg/ml (our unpublished data). As this is a retrospective study, fosfomycin MICs were not determined. Since fosfomycin prostate levels are around 4 μg/g of tissue, and some isolates may have had MICs of >4 μg/ml, this may be the reason for some failures. We concur with other authors (12, 17, 18) who suggest that fosfomycin should not be used for treating CBP caused by microorganisms with MICs of ≥4 μg/ml. Another factor to consider is that fosfomycin activity is higher in an acidic environment, but the pH is alkaline in CBP (around 8.5), which might lead to decreased activity of the drug (18). Lastly, prostatic calcifications were present in 4/7 (57%) patients with microbiological failure. CBP is now considered a biofilm infection (18–21), and bacteria present in calcification biofilms are difficult to eradicate, potentially leading to therapeutic failure.

To our knowledge, this is the first series of CBP patients treated with oral FT; hence, we had no precedence to guide drug dosing and duration for this condition. We choose 6 weeks of FT, because that is the generally recommended duration of CBP treatment (1–3, 17). The successful treatment of 2 prostatitis patients with 12 to 16 weeks of FT at 3 g/24 h was recently reported (12). We initially administered FT at 3 g/72 h, the recommended dose for

**TABLE 1** Clinical and microbiological data, therapeutic aspects, and outcomes of chronic bacterial prostatitis patients treated with fosfomycin-tromethamine

| Case no. | Age (yr) | Comorbidity[a] | Age of first UTI (yr)[b] | No. of previous episodes | No. of previous urine cultures with same bacterium | Previous semen culture result | Previous AB failure(s)[c] | Previous duration of AB treatment (wk) | Etiology | MDR mechanism[d] | Susceptibility to[e]: CIP | SXT | Clinical cure | Microbiological eradication | Follow-up (mo) | Failure result (time to relapse [mo]) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 80 | Asthma, CKD | 0.9 | 4 | 4 | ND[f] | ETP (1 g/24 h) | 4 | *E. coli* | AmpC producer | R | R | Yes | Yes | 36 | |
| 2 | 52 | | 22 | 7 | 4 | ND | CIP | 8 | *E. coli* | ESBL producer | R | R | Yes | Yes | 54 | |
| 3 | 54 | | 17 | 12 | 4 | ND | SXT | 12 | *E. coli* | ESBL producer | R | S | No | No | | Persistence |
| 4 | 54 | G6PD deficiency | 13 | 9 | 2 | ND | CIP | 4 | *E. coli* | | R | R | No | No | | Relapse (1) |
| 5 | 31 | | 2 | 3 | 2 | ND | CIP + SXT + CXM | 6 | *E. coli* | | R | S | No | No | | Relapse (3) |
| 6 | 29 | CVID | 3 | 5 | 3 | Positive | CIP | 6 | *E. coli* | ESBL producer | S | S | Yes | Yes | 22 | |
| 7 | 57 | DM | 1 | 4 | 2 | Positive | CIP | 6 | *E. coli* | | R | R | Yes | Yes | 16 | |
| 8 | 22 | | 0.8 | 2 | 2 | Positive | CIP | 4 | *E. coli* | | R | R | Yes | Yes | 14 | |
| 9 | 44 | | 3 | 10 | 3 | Positive | CIP | 6 | *E. coli* | | S | R | No | No | | Relapse (1) |
| 10 | 59 | | 1 | 4 | 4 | ND | SXT | 6 | *E. coli* | ESBL producer | R | S | Yes | Yes | 20 | |
| 11 | 49 | | 15 | 4 | 2 | Positive | AMC (875 mg/125 mg/8 h) | 4 | *E. coli* | | R | R | No | Yes | 14 | |
| 12 | 58 | | 20 | 9 | 2 | ND | CIP | 6 | *K. oxytoca* | | S | R | No | No | | Relapse (1) |
| 13 | 70 | HT, COPD | 12 | 5 | 4 | ND | SXT | 12 | *E. coli* | | R | S | No | No | | Relapse (1) |
| 14 | 65 | | 6 | 4 | 3 | Positive | CIP | 12 | *E. coli* | | S | S | No | No | | Relapse (1)[g] |
| 15 | 54 | | 8 | 4 | 2 | Positive | CIP | 6 | *E. coli* | | S | S | Yes | Yes | 12 | |

[a] CKD, chronic kidney disease; G6PD, glucose-6-phosphate dehydrogenase deficiency; CVID, common variable immune deficiency; DM, diabetes mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease.
[b] UTI, urinary tract infection.
[c] AB, antibiotic; ETP, ertapenem; CIP, ciprofloxacin; SXT, trimethoprim-sulfamethoxazole; CXM, cefuroxime; AMC, amoxicillin-clavulanate.
[d] MDR, multidrug resistant; ESBL, extended-spectrum β-lactamase.
[e] R, resistant; S, susceptible.
[f] ND, not done.
[g] *E. coli* relapse and *Klebsiella pneumoniae* superinfection.

uncomplicated UTI, because of concerns that dosing daily or every 48 h might increase gastrointestinal side effects (22). When we started using FT, there was only one reported case of vancomycin-resistant enterococcal prostatitis successfully treated with oral FT at 3 g/72 h for 21 days (23). Because the 72-h dose had been well tolerated, we used FT every 48 h in 1 patient who relapsed and in our last 2 cases. These data and the good tolerance reported by Grayson et al. (12) suggest that a shorter dosing interval may be feasible. Nonetheless, a regimen of 3 g/12 h has been associated with gastrointestinal side effects (12). Further studies are needed to establish the optimal dose and duration of FT in CBP.

Fosfomycin, an old drug recently rediscovered for the treatment of multidrug-resistant infections, has a success rate of >90% for lower UTI (8–10, 17). Interestingly, in our limited experience with MDRE CBP, 4/5 (80%) patients had sustained clinical and microbiological eradication. These data add further information to the recent case reports of MDRE prostatitis successfully treated with fosfomycin (12, 18), making FT a promising antibiotic in the current scenario of an increasing incidence of MDRE infections.

This study is limited by its retrospective, single-center, and noncontrolled design, a small sample size, and uniform management by one of the authors (C.P.), limiting the generalizability of the results. Furthermore, clinical response evaluations are subjective, and the Meares-Stamey test (four-glass test), which is considered the diagnostic reference standard, was not systematically employed, as it is a cumbersome method that is used little in clinical settings (24). Semen culture used in our study has a sensitivity similar to that of the four-glass method (25), and because of its high specificity (94%), some authors consider it sufficient for initiating antibiotics in symptomatic patients (26). We believe it is unlikely that the microbiological relapse rate in our study would have been higher if the 4-glass test had been used, as our patients had a lengthy clinical follow-up period (>1 year).

All patients met the clinical criteria for CBP (recurrent UTI and symptoms for >3 months), had several positive cultures with the same *Enterobacteriaceae* organism, and had failed >4 weeks of appropriately active antibiotics at an adequate dosage. Therefore, the clinical diagnosis of CBP can be considered reliable. The fact that FT administration is simple, well tolerated, and cost-effective is a strength of our results. Other alternatives to ciprofloxacin and co-trimoxazole require more-complex and non-evidence-based antibiotic regimens (long-term suppressive or intravenous antibiotics).

In conclusion, FT may be considered an alternative treatment for CBP in patients with MDRE infection and resistance or side effects to first-line drugs. Until further data are available, it would be prudent to use this option only for isolates with fosfomycin MICs of ≥4 μg/ml.

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